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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/922,568 | 08/03/2001 | Udo Baron | BBI-088CPADV2 | 9670 |
| 959 | 7590 | 01/16/2004 | | |
| LAHIVE & COCKFIELD, LLP. 28 STATE STREET BOSTON, MA 02109 | | | EXAMINER QIAN, CELINE X | |
| | | | ART UNIT 1636 | PAPER NUMBER |

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/922,568

Applicant(s)

BARON ET AL.

Examiner

Celine X Qian

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 October 2003.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 32-54 is/are pending in the application.
- 4a) Of the above claim(s) 33-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32 and 40-54 is/are rejected.
- 7) ☒ Claim(s) 52-54 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 August 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Claims 32-54 are pending in the application. Claims 33-39 are withdrawn from consideration for being directed to a non-elected subject matter. Claims 32 and 40-54 are currently under examination.

This Office Action is in response to the Amendment filed on 10/15/03.

Response to Amendment

The rejection of claims 32 and 40-50 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

Claims 32, 40-50 and newly added claims 51-54 stand rejected under 35 U.S.C. 112 1st paragraph for reasons set forth of the record mailed on and further discussed below.

Claim 51 is rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Claims 52-54 are objected to for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32 and 40-54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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In response to this rejection, Applicants argue that the instant specification teaches how to make the claimed transgenic and homologous recombinant animal. Applicants further argue that the state of art at the time of filing supports successful generation of transgenic animal. Applicants assert that the Mullin reference demonstrate the technology for successful generation of a transgenic sheep is available at the time of filing. Applicants further quote the reference stating that the generation of transgenic mouse is only a guide to the potential success of a transgene construct in other species in some cases, and assert that the specification (page 11, lines 34-36) teaches that the design of expression vectors depending on particular host cell. Applicants assert that Seidel et al. also demonstrate the technologies for making non-mouse transgenic animal is available at the time of filing because making such transgenic animals is at most more time consuming or more problematic from a logistic standpoint. Moreover, Applicants assert that the Hammer reference is too old to represent the predictability of transgenic animals at the time of filing. Further, Applicants argue that this reference does not teach that the phenotypic differences between rats and mice is due to differential expression or activity of the B27 transgene in these animals due to the unpredictability of transgene expression and integration, rather, it demonstrate that a transgene is successfully expressed in two different species. Finally, Applicants assert that the state of art at the time of filing teaches successful generation of transgenic animals, and list references A-G to support this point. Applicants further indicate that a search of pub-med database with "transgenic and mice" resulted in 2,220 hits, again supports the notion that the state of art at the-time of filing teaches successful generation of transgenic animals. Applicants therefore conclude that the claimed invention is enabled.

Applicants' arguments have been fully considered, but they are not persuasive. The claimed invention is not enabled by the instant specification for reasons set forth of the record mailed on 7/15/03. Applicant appears to misconstrue that the rejection is based on the assumption that making a transgenic animal is unpredictable at the time of filing. In fact, the rejection is based on how to make and use the invention in commensurate with the scope of the claim. The phenotype of the claimed transgenic animal is essential to the enablement of the claimed invention because one skilled in the art would not know how to use a transgenic animal with claimed genotype, but shows no phenotypic feature. However, it is such phenotypic features in any given species of a transgenic animal cannot be accurately predicted at the time of filing. Mullin et al. teaches that the major problem regarding pronuclear injection (as suggested by the specification) is that the exogenous DNA integrates randomly into chromosomal DNA. Positional effects, where the transgene is influenced by its site of integration in the host chromosome can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number-independent expression and complete silencing of the transgene. Such problem would affect the level of expression of the fusion protein in the transgenic animal, thus it is unpredictable whether the claimed transgenic animal would produce the fusion protein at high enough level that can regulate the transcription of another gene and produces a phenotype. The specification at page 11, lines 34-36 only teaches that CMV E1 promoter can be used in different host cells. Such teaching does not overcome the unpredictability discussed above.

Similarly, Applicants' argument that the Seidel reference demonstrates that transgene expression is achieved in cattle, goats, sheep, and swine does not overcome the unpredictability

of making a transgenic animal with predicted phenotype for same reasons discussed above. The problems discussed by Seidel in making transgenic livestock also contribute to such unpredictability. Like Mullin et al., Seidel also discuss the problem of positional effects such as integration on the X-chromosome, multiple sites of insertion, genetic imprint and insertional mutagenesis (see page 27, 2nd and 3rd paragraph).

Although Hammer et al. were published before the filing of this application, the problem discussed in the article is not solved at the time of filing, therefore, it is still relevant to support that the phenotype produced in one species of animal is not predictive for the same phenotype in another species. If Applicants dispute this notion, Applicants must provide evidence that such unpredictability is resolved at the time of filing. Applicants are reminded that the previous office action does not make the assertion that Hammer et al. teaches transgenic mouse unable to display diseased phenotype due to differential expression of the transgene than that of the rat, rather, it states that integration of a transgene into alternative species may result in widely different phenotypic responses. This is an example of a specific phenotype in one species is not predictive of the same phenotype in another species.

Finally, the 2220 hits generated by searching PubMed with the term "transgenic and mouse" by itself at most indicates that there are quite large amount of research focuses in this area. Contrary to Applicants' assertion, this information does not enable the claimed invention, especially the claims are not limited to transgenic mouse. The references (A-G) provided by Applicants are fully considered, they also fail to provide any support that the discussed unpredictability is overcome at the time of filing.

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With regard to the newly added claim 51, it is drawn to a homologous recombinant non-human transgenic animal. It is interpreted as a transgenic animal made by the method of homologous recombination in ES cells and further developed into a transgenic animal upon transplantation into blastocyst. Applicants are reminded that only mouse ES cells are available at the time of filing. Therefore, the claim is not enabled to its full scope since it encompasses all kinds of animals.

In summary, in view of the unpredictability discussed in the previous office action and above, the claimed invention is not enabled by the instant specification. Therefore, this rejection is maintained.

New Grounds of Rejection Necessitated by Applicant's Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "homologous recombinant non-human transgenic animal" renders the claim indefinite because it is unclear what this term encompasses. Does it mean that the non-human transgenic animal is made by homologous recombinant and ES cell technology or said animal comprises a cell that has undergone homologous recombination? Or is there homologous recombination events taking place in said animal?

Double Patenting

Applicant is advised that should claims 40-42 be found allowable, claims 52-54 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.

Anne-Marie Falk
ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER